intestinal flora attack the large intestine—appendicitis and diverticulitis." He goes on to say that the relation of bacillary dysentery to ulcerative colitis is "altogether peculiar." "The two diseases are closely allied and may be one and the same. Even if not the same, the pathology of dysentery has a very direct bearing on the subject." He finds, however, that there is no substantial evidence in favor of the theory, and he finds it difficult to accept favorable serum therapy as confirmation.

Mackie[6] has given an excellent review of the relationship of dysentery bacilli to chronic ulcerative colitis, and has reported one case of the latter with heavy infection of Flexner-Y bacilli which was completely cured by autogenous vaccine. In discussing this case, he notes that the Flexner-Y group of dysentery bacilli may cause mild clinical attacks which may not be epidemic. This is fully in accord with our own and other published experience. Mackie notes further that some such cases may become chronic, with lower bowel ulceration, even though the initial attack was very mild. He calls attention to the similarity or identity in kind of the lesions of chronic bacillary dysentery and many cases of chronic ulcerative colitis, and remarks on the intermittance of the shedding of bacilli as a characteristic of chronic Flexner-Y type infection.

In discussing the relationship of chronic ulcerative colitis to chronic bacillary dysentery, Mackie[7] notes frequent involvement of the small intestine, which then shows motor changes suggestive of acute exudative inflammation. In eighty-three cases, he recovered dysentery bacilli in 20.4 per cent, and obtained serologic evidence in an additional 21.6 per cent. In 102 controls, dysentery bacilli were recovered in two and positive agglutination was present in seven. He concludes that the evidence does not support the idea of a unitary cause of chronic ulcerative colitis, but he considers that a certain group of cases are due to chronic infection with dysentery bacilli.

Penner[8] believes that the available evidence indicates that about 10 to 15 per cent of cases clinically diagnosed as idiopathic ulcerative colitis, rightfully belong in the group of chronic bacillary dysentery, and the remainder are still of unknown etiology. He notes the preponderance of ulcerative colitis in the third and fourth decades, and its rarity in childhood, when bacillary dysentery is most common. Its occurrence, twice as often in women as in men, is against a bacillary cause, and also the relative infrequence of chronic ulcerative colitis among the males of central Europe, where bacillary dysentery was exceedingly prevalent during the Great War. He comments also on the noncontagiousness of chronic ulcerative colitis.

Felsen[9] attempts to relate nonspecific ulcerative colitis, acute bacillary dysentery, distal ileitis, ileitis and nonspecific granuloma, as various stages of one disease. He notes that cases of acute bacillary dysentery, lasting more than three weeks, seemed to persist due to nonspecific secondary infection. Much of his diagnosis, as in the case of many other writers, was based on blood agglutinations which are notoriously unreliable, if not useless. Felsen[10] admits that in nonspecific ulcerative colitis, the specific organism has usually died out and been replaced by secondary invaders, usually an enterococcus and B. coli.

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(To be continued)

WHAT CAN ONE EXPECT FROM RADIATION IN CARCINOMA OF THE RECTUM AND ANUS?*

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DISCUSSION *by William H. Daniel, M. D., Los Angeles.*

I AM sure that every one of us has been confronted by patients who have had cancer of the terminal portion of the intestinal tract and who have asked, What may I expect from x-ray and radium therapy? Such a question is logical and one that should be answered with ease, especially since radiation has been a method of treatment in carcinoma for over thirty years. However, it is much more difficult than it first seems. In order to answer the question intelligently, it will be discussed in two parts—as it applies to carcinoma of the rectum, and to carcinoma of the anus. Though these forms of cancer are both found in the lower 15 centimeters of the large bowel, the problems involved are distinct as to anatomic relations and spread, and as to histologic structure.

COMMENTS ON THE LITERATURE

In reviewing the radiologic literature, one is struck by the absence of any appreciable mention of five-year cures. Sheddan, in reviewing the use of radium in rectal cancer, and presenting his results, has no five-year cures, but has two patients living at three and four years, respectively, with no evidence of disease. He mentions the various techniques used throughout the world, and he lists

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nine—evidence of the fact that no one of them is satisfactory. Bowing and Fricke report sixteen three-year cures and five five-year cures out of 286 cases. The workers in St. Mark's Hospital in London, namely, Lockhart-Mummery and Sir Charles Gordon Watson, used radium alone in a series of cases. Their results were very disappointing, since they had no five-year cures. However, the method of using radium was largely through the technique of Neumann and Coryn, in which the coccyx is removed and the bowel exposed so that platinum needles containing radium are implanted outside the rectum at the level of the tumor. Such a procedure is almost as formidable as the radical operation and has resulted in much postoperative shock, with death from the operation in some instances or a slow painful convalescence, usually complicated by prolonged infection, sloughing, and frequent recurrences. Mummery says that this procedure has been given up; and though he cites no five-year cures, he has had recoveries in early cases where he has used gold radon seeds intrarectally. Brinkley has also reported five-year recoveries following radon seeds and x-radiation at the Memorial Hospital.

AUTHOR'S OBSERVATIONS

In reviewing our experience during the past fifteen years, our results are similar to those obtained by other workers in this field. During that time we have treated 237 cases, which fell into the following groups:

(*a*) Inoperable: 167 cases, 40 of whom had colostomies.

(*b*) Recurrent: 32 cases, all of whom had had radical excision of the rectum.

(*c*) Operable: 38 cases, three of whom had colostomies.

In these patients no definite or set technique was followed. In the early cases many of them were inadequately treated, according to our present-day conception. We had no past experience to fall back upon, and the dosages used compared favorably with those employed in other parts of the body. Some were treated with low voltage x-ray, others with high voltage x-ray, while at present we are using supervoltage x-rays. Likewise, when surface applications of radium were used the radium was filtered through brass and rubber, while now it is filtered through gold and rubber. Some had interstitial radiation obtained from steel needles, but at present needles are used with .5 millimeter of platinum. Finally, some were treated with radon seeds made up with glass, but now these are of gold. We had no definite idea as to tumor dosage, since our conception of radiosensitivity was hazy. No accurate attempt was made to estimate the radiation absorption in the tumor obtained from either external or surface radiation. Even at that we did obtain some results that were encouraging.

INOPERABLE GROUP

In these patients one cannot hope for anything but palliation, as manifested by (*a*) diminution in size of the tumor; (*b*) relief from pain; and (*c*) cessation of bleeding, with resultant prolongation of life; for even in massive pelvic involvements the degree of benefit has at times been striking. The average length of life after the patient was first seen was one year, though many were followed for two and a half years and some for as long as four years before they succumbed to liver metastasis. Those patients who had colostomies did much better than the others, as radiation therapy could be carried out more effectively since infection was less and the bowel was at complete rest. In those individuals refusing colostomies, we resorted to electrocoagulation through the proctoscope. While the immediate results are good as far as the obstruction is concerned, fibrosis and contracture take place later which necessitates its repetition on one or more occasions. The occasional use of radiation preoperatively, especially radium, has resulted in transforming an inoperable case to an operable one. Bowing and Fricke speak of its use in this connection. Whether these patients exhibit a low rate of recurrence and a high rate of five-year curability is too early to state.

The histories of the following patients in this group are of interest.

REPORTS OF CASES

CASE 1.—E. D. A. Seen in 1929. Sixty years of age. Complains of rectal bleeding and backache. Two months ago he had a colostomy elsewhere for obstruction and a carcinoma was found that had involved the posterior wall of the bladder, the prostate, and the sacrum. He was given three courses of high voltage x-ray therapy and two applications of radium in the rectum, filtered through brass and rubber. His bleeding and pain disappeared; he gained weight. He played golf every day, and was comfortable up to six months before he died—four and a half years after he was first seen.

* * *

CASE 2.—J. F. D. First seen in 1932. Age, 51. He had had rectal bleeding for six months. Twelve days ago his physician had cauterized the growth and a colostomy was done. He was given supervoltage x-ray therapy and radium therapy in the form of radon seeds. He lived in comfort, carrying on his work as a pattern maker for three and a half years, when he died of liver metastasis.

* * *

CASE 3.—H. G. First seen in 1933. Age, 55. He had rectal bleeding for four months. Two weeks earlier his surgeon had cauterized the growth, and a colostomy was done. Histologically, it was an adenocarcinoma, Grade IV. He was given two courses of supervoltage x-ray therapy, and radon seeds were plunged into the growth. He lived in comfort for two and a half years, when he suddenly died of brain metastasis. Autopsy revealed that the rectum was free from any evidence of carcinoma, grossly and microscopically.

* * *

CASE 4.—B. D. First seen in 1936. Age, 50. Complained of intense backache and rectal bleeding of four months. Rectal examination showed a tumor mass partially obstructing the rectum, fixed to the anterior wall of the sacrum. Histologically, the tumor was an adenocarcinoma, Grade II. He was advised to have a colostomy, which he refused. He was given two courses of supervoltage x-ray. Radium platinum needles were plunged into the base of the tumor after the obstruction was relieved by electrocoagulation. Pain and bleeding ceased, and for two years he has been comfortable. He gradually developed an obstruction which necessitated a colostomy at the Veterans' Facility, where he died a week after the operation.

RECURRENT GROUP

In this group treatment was given to control growth and to relieve pain. All patients died within

a two-year period, usually from infection in the operative field, though a few died from liver involvement.

OPERABLE GROUP

Here the problem is different. The lesion may be large or small and is not fixed. Our experiences in this group have been obtained by the use of radiation alone, or combined with electrocoagulation and colostomy. The following histories illustrate the point.

REPORTS OF CASES

CASE 5.—Mrs. R. P. First seen in 1930. Age, 65. Three months ago she noticed rectal bleeding. There was a lesion two centimeters wide on the posterior wall of the rectum. Histologically, it was an adenocarcinoma, not graded. Radon seeds were implanted with disappearance of the tumor. She remained well until in February, 1938, when she died of liver metastasis. Locally, there was no evidence of tumor.

CASE 6.—A. A. First seen in 1927. Age, 44. Complained of rectal bleeding of seven months' standing. Two weeks before, his physician had partly destroyed an adenocarcinoma with the cautery. Radium, filtered through brass and rubber, was placed on the base. A severe reaction took place, but the patient recovered and was living in 1938.

CASE 7.—Mrs. P. D. First seen in 1935. Age, 45. For three years she had had rectal bleeding. A biopsy showed an adenocarcinoma. The surface of the tumor was cauterized, and radium, filtered through gold and rubber, in a surface application, was placed against it. At present she is well, two and a half years, with no evidence of tumor.

In this group we have also two individuals, both patients of Dr. E. C. Moore, on whom preliminary colostomies were done, after which radium was used.

CASE 8.—Mrs. E. C. First seen in 1937. Age, 55. She had an adenocarcinoma 3 by 4 centimeters, 3 centimeters above the sphincter. Platinum needles, containing 2 milligrams each, were inserted beneath the tumor, with complete disappearance of the growth. This patient has been well one year and her colostomy has been closed.

CASE 9.—W. L. First seen in 1937. Age, 63. He had a rectal tumor 2 centimeters in diameter, which was an adenocarcinoma. After colostomy, platinum needles, containing radium element, were inserted into the base of the tumor, and this was followed by its complete disappearance. His colostomy has been closed.

EPITHELIOMA OF THE ANUS

Carcinoma of the anus, which is really epithelioma of the anus, is discussed separately from the rectum, since the growth is of a different variety histologically, and because it metastasizes to the inguinal nodes, rather than to the lumbar nodes. It is accessible and, as such, may be removed by surgery or cautery with good results, but this usually results in destruction of the sphincter with its loss of control. Since epitheliomas on the skin, in the mouth, and on the cervix are successfully controlled by radiation, we feel that they can be treated just as successfully at the anal margin by the same method. Combined x-radiation with interstitial or surface radium in our hands have been very successful, as illustrated by the cases listed below. Even Mummery, who is an advocate of the radical operation for carcinoma of the rectum, says that epithelioma of the anal region is better treated by radium, and in such cases he always advises radium.

Our experience in this type of case is limited to twelve patients. Of these we have adequate records in nine. Two of the patients were advanced and died of metastasis after the primary lesion was controlled. The others all had complete disappearance of their tumors and have been followed from two to seven years. They are in good health and have complete control. The following histories are typical of this group.

REPORTS OF CASES

CASE 10.—Mrs. F. L. First seen in 1932. Age, 65. Inside the anal margin is a nodular bleeding tumor 3 by 3 centimeters. Section shows it to be a squamous-cell epithelioma, Grade III. She was given a course of high voltage x-ray, and radium, filtered through gold, was applied to the base. Except for a stricture she has been well for six years.

CASE 11.—E. W. R. First seen in 1934. Age, 68. For three years he has had a prolapse of the rectum. Recently an ulcer came on and biopsy showed that it was due to a squamous-cell epithelioma. Platinum needles were inserted around the anal margin. There was complete healing of the ulcer, with no anal disturbance. He is well now almost four years.

CASE 12.—Mrs. F. K. First seen in 1936. Age, 52. Three months ago she began to have rectal bleeding and pain. On the anterior rectal wall, involving the sphincter, there was a bleeding tumor mass 4 centimeters in diameter. Section showed it to be a squamous-cell epithelioma, Grade III. She was given a course of supervoltage x-ray, and platinum needles, each containing 2 milligrams of radium, were inserted under the base. There was complete healing and for two years she has been well.

CASE 13.—W. B. M. First seen in 1935. Age, 77. He has had fistulae and discharging sinuses around the anus for many years. He had a nodular infiltrating tumor completely surrounding the anus. It was 12 by 15 centimeters, and there were multiple fixed nodes in both groins. Histologically, it was squamous-cell epithelioma, Grade II. He was treated by supervoltage x-ray alone. The primary tumor disappeared, though the patient died six months later of general metastasis.

COMMENT

Despite the fact that rectal carcinoma carries an operability of only 50 per cent, and radical resection is followed by a mortality varying from 10 to 50 per cent—depending upon the type of operation—surgery offers the greatest hope of recovery. While many patients have recovered from radiation alone, they are the exceptional case and not the rule. However, up to the time that the radical operation was standardized, surgical end-results were extremely unsatisfactory, not only from the viewpoint of mortality but also from the standpoint of recurrence and five-year end-results. So, too, with radiation therapy: the technique has been in a flux, constantly changing, as our ideas of carrying out the procedure have changed. We now have improved equipment which will give greater depth doses from x-ray, while our knowledge of radiation effects and sensitivity have progressed greatly in the last decade. For these reasons one should expect better results in the future.

From a statistical viewpoint, the crux of the question is dependent on what the definition "oper-

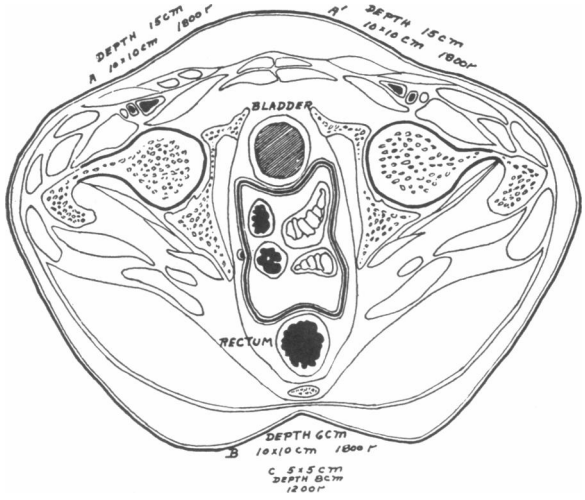

Fig. 1.—Section (male) above symphysis pubis.

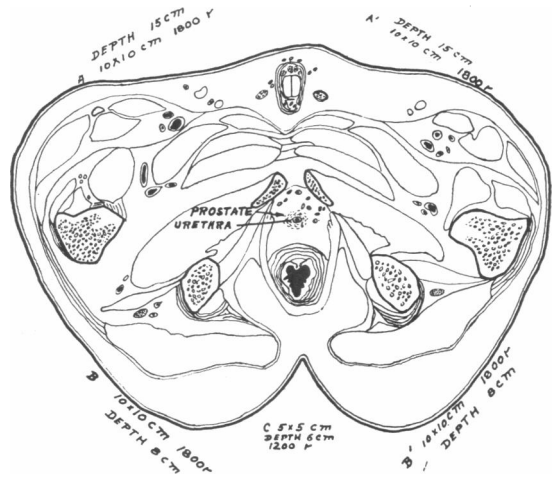

Fig. 2.—Section (male) below symphysis pubis.

ability" means. This must be based on not only the extent and size of the lesion, but also the pathological grading of the tumor. Tumors graded III and IV are obviously more prone to recurrence than I and II when attacked surgically. As a matter of fact, a patient with a Grade IV tumor, no matter how early it is recognized, does not recover from a surgical attack, but the tumor will disappear after radiation. What constitutes "operable," then, is a matter of personal judgment. Obviously, patients who develop and die from recurrence locally were operable technically at the time of operation, but histologically not.

Curability.—Curability, as defined in the literature, is based on operability. All statistics are based on this factor—ignoring the vast host of patients who do not fall into this group. The patient who comes into your office, and who knows that he has cancer, is not interested in what artificial classification he falls into; he wants to know what can be done! (All statistics should be based on absolute figures.) Viewed in this manner, then, the quoted curability figures would be decreased by 50 per cent, and would only run from 10 to 15 per cent. While surgery does give us a better outlook in the strictly operable case, especially in Grades I and II tumors, it is time that both surgeon and radiotherapist should no longer be rivals but allies in this field. When Grades III and IV tumors are under investigation, the radiotherapist should be consulted before the operation regarding preoperative treatment in these groups; and, if possible, he should be an assistant so that he can be fully familiar with the existing conditions in the particular patient under consideration.

Adenocarcinomas in this region are deep-seated and are more or less inaccessible. While they have the reputation of being radio-resistant, I do not believe that cells of this type in this region differ greatly from those found in the breast or the uterus. Many will be found to be sensitive; the difficulty rests in getting enough radiation into the desired area. Knowing that squamous cell epitheliomas need about ten erythema doses to destroy them, it is reasonable to assume that adenocarcinomas will need this and more. Such dosage will naturally result in more or less fibrosis. Since the bowel wall is only 2 or 3 millimeters thick, and if the lesion is encircling and infiltrates the circular muscles, its disappearance will be followed by stricture formation and partial obstruction.

In order to attain a proper dosage, it is necessary to get the benefit of both x-ray and radium. This can be done by an estimation of the location of the tumor so as to be able to calculate the dosage from x-radiation. Referring to Figures 1 and 2, which represent tumors in two different locations in the rectum, we may see what must be expected. If four or five ports be used with 1800 r to each port, except the perineal, then a tumor dosage of three and a half erythema doses is obtainable in the average individual. If one desires, one may push the total dosage up to the skin-tolerance dose of 2400 or 3000 r over each port, with corresponding increase in tumor dose; but this may be followed by late undesirable sequelae in the skin and in the bladder. The difference between ten erythemas and three and a half or six and a half erythema doses must then be made up by the use of radium. Whether one should use radium as a surface application or interstitially, as radon or in platinum needles, will depend on the individual case; its dosage is easily calculated from the Quimby-Martin tables.

Colostomy.—While many patients may be successfully treated without a colostomy, the more one sees these individuals the more one feels that a preliminary colostomy should always be done with the understanding that if the treatment is successful and there is no fibrous stricture, the colostomy may be closed after a year. The colostomy puts the rectum at rest, the inflammation subsides, and the danger of infection and radiation necrosis is reduced to a minimum. Furthermore, since peristalsis and the presence of fecal matter is done away with, it is much easier to retain the radium in the desired location as long as it is needed.

With such improvements in technique, many operable cases of rectal cancer may be justifiably treated by radiation under the following conditions:

(*a*) Where the patient refuses operation.

Fig. 3

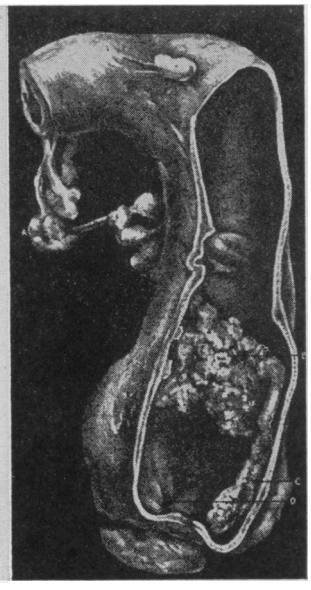

Fig. 4

(*b*) Where age and other complications preclude the radical operation.

(*c*) In the operable patient who has a small tumor of high-grade malignancy, which does not encircle the bowel and one in whom the proctoscope passes by readily. Here adequate dosage sufficient for complete destruction is obtainable by radon seeds or platinum needles. However, those operable cases that do not allow the passage of the proctoscope are not particularly suitable, since one cannot estimate the extent of the disease—as shown in Figures 3 and 4. In them it is impossible to use radon seeds with accuracy. Surface applications may be used, but the size of the area to be treated and the dosage must be a matter of conjecture. If radium is used in a contact applicator in order to get depth effect in a tumor from one-half to one centimeter thick, caustic effects are obtained on the surface, which add to the difficulties, as it results in necrosis, infection and rectal tenesmus. Since rectal cancers are slow-growing, and it has been estimated by various observers that a year elapses before the disease passes beyond the muscular coat, a trial of radiation, especially radium locally, will not jeopardize the patient's chances of recovery. If the radiation does not control the growth, the radical operation can still be carried out.

SUMMARY

In carcinoma of the rectum, radiation will stop bleeding and relieve pain in the majority of individuals. Occasionally, the inoperable case may become operable following its use. Though radiation therapy has been disappointing in the operable case when, computing five-year cures as compared with radical surgery, many patients are cured by its use; however, the percentage is not large. This may be improved by paying more attention to histologic structure of the tumor, by developing a better technique and by careful selection of suitable cases. Where treatment is contemplated, colostomy should be carried out, if possible, in operable as well as in inoperable cases.

In epithelioma of the anus, radiation stands on a par with surgery in end-results. While successful surgery invariably results in destruction of the sphincter, radiation is preferable, as the curability is high and sphincter control is retained. Therefore, radiation therapy should be the method of choice in this region.

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DISCUSSION

WILLIAM H. DANIEL, M. D. (1930 Wilshire Boulevard, Los Angeles).—We all regret that radiation has not given us the results in carcinoma of the rectum that we had hoped for. Very thorough and detailed treatment has been carried out by many workers in different parts of the world. The results reported correspond very closely to those Doctor Meland has recounted here. I have seen several patients who have been treated with deep therapy and who remained fairly comfortable for several months or longer. There is still some variance of opinion whether radiation will affect the metastases at some distance from the tumor. There is also dispute as to the value of preoperative and postoperative treatment.

My personal experience with radiation treatment has been limited. I have had the opportunity to follow some cases treated by this means, and some cases which had had only preoperative radiation and some postoperative radiation. Several years ago, when the high voltage was first used, I was not impressed with the results. With the newer methods of treatment, I am convinced that there is value in selected cases, and I am positive there is a field for this procedure in the poor risk, or inoperable case. In cases that are distinctly operable, or borderline, I still feel that surgery alone is the best procedure.

In epithelioma of the anus, which constitutes less than 5 per cent of the total, I have been convinced that radiation by radium and x-ray is to be considered as efficacious as surgery alone. My results with surgical treatment, even with radical procedures, have been disappointing due to recurrence or early metastases. These cases are apparently more malignant than the adenocarcinoma. A combination of radiation and surgery might, in these cases, answer the problem.

SULFANILAMIDE: SOME IMMUNOLOGICAL STUDIES*

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DISCUSSION *by John Dougherty, M. D., Oakland; Albert M. Meads, M.D., Oakland; Angus Wright, M.D., Los Angeles.*

THE history of sulfanilamid dates back to 1908 when Gelmo,[1] a German dye chemist, synthesized the compound for that industry. In 1909, Hoerlein, Dressel, and Kothe[2] prepared the first azo dye stuffs with sulfanilamid radicles, but no pharmacological investigations were conducted. In 1917, Jacobs and Heidelberger,[3] of this country, synthesized meta-amino-benzene-sulfonamid and para-chlor-acetyl-amino-benzene-sulfonamid, and combined it with hydrocuprein through the azo linkage.[4] They stated that their colleague, Dr. Martha Wollstein, would discuss the bactericidal properties of these drugs in a subsequent paper. This, unfortunately, was never published. In 1932, Mietzsch and Klarer[5] patented a new dye now known as prontosil. Domagk,[6] working in conjunction with these dye chemists, demonstrated the therapeutic value of prontosil rubrum in mice

* Read before the Pathology and Bacteriology Section of the California Medical Association at the sixty-seventh annual session, Pasadena, May 9–12, 1938.